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Salbutamol Responsive Fetal Acetylcholine Receptor Inactivation Syndrome

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Introduction

Transient neonatal myasthenia gravis (TNMG) is a rare and usually self-limiting condition due to maternal acetylcholine receptor (AChR) antibodies in neonates born to mothers with myasthenia gravis (MG). However, a skeletal myopathy with consistent and recognizable features (termed “fetal acetylcholine receptor inactivation syndrome” or FARIS) was recently reported in some patients [1,2]. FARIS occurs in association with clinically manifest maternal MG, or asymptotically elevated maternal AChR antibodies directed against the fetal AChR γ subunit. Whilst *in utero* antibody exposure is considered the main pathogenic mechanism, the timing and intensity of maternal MG treatment plays an important role in determining fetal and postnatal outcome [1].

The clinical spectrum of FARIS is wide, ranging from lethal arthrogryposis multiplex congenita (AMC) to mild, mainly facial myopathic manifestations persisting into adulthood [1,3]. Whilst the symptoms of typical TNMG often respond to acetylcholine esterase inhibition or removal of causative antibodies, FARIS does not respond to the same treatments, likely reflecting antibody-mediated structural endplate alterations of antenatal onset, given that the γ -subunit is required for the assembly of pre-patterned AChR clusters and, ultimately, neuromuscular synaptogenesis [4].

We report a child with FARIS showing dramatic symptom improvement following therapy with salbutamol (albuterol), a short-acting β 2-adrenergic receptor agonist previously used effectively in specific genetic forms of congenital myasthenic syndrome (CMS).

Case Description

The proband (Patient 2.2 in [1]) is the second child of a previously reported family affected by FARIS [1,5]. His mother was diagnosed with MG in her first pregnancy. He had an older sibling with lethal AMC, and a younger brother with much milder symptoms, probably reflecting different treatment intensities of maternal MG over

consecutive pregnancies. He was intubated at birth and ventilated for 3 weeks. He was profoundly hypotonic with a weak fatigable suck and required nasogastric tube feeding, followed by temporary gastrostomy for 9 months. Early examinations revealed motor delay and marked axial, facial and bulbar weakness. He received pyridostigmine from birth until his second year, with little benefit beyond 2-3 months. Despite appropriate developmental milestones at 20 months he had persistent facial diplegia with severe oromotor language difficulties, a weak voice, drooling, and substantially reduced stamina.

Examination at almost 5 years demonstrated severe facial muscle weakness, with an open mouthed expression (Figure 1A), a high arched palate, bilateral ptosis, and limited upgaze. His voice was dysarthric, dysphonic and weak (sentences only understood by his mother). Antigravity movements in neck flexion were limited (MRC grade 3-/5) but power was normal in all other muscles. There was no added fatigability. He was treated with oral Salbutamol (Albuterol) at an initial dose of 1mg three times daily. Within 48 hours a dramatic improvement in facial expression and definition including ptosis (Figure 1B), quality of voice and speech (now understood by most adults), general stamina (significantly reduced rest periods) and drooling frequency was noted. Salbutamol was increased to 2mg three times daily, resulting in further improvement (Figure 1C), confirmed on examination at 4 years 9 months. Neck flexion was MRC3+/5. Salbutamol benefits were sustained and treatment tolerated well.

Conclusion

Fetal acetylcholine receptor inactivation syndrome (FARIS) [1,2] is a recently recognized, early-onset myopathy due to maternal antibodies against the fetal AChR γ subunit which is crucial for the normal development and functioning of the embryonic neuromuscular junction (NMJ), a notion also supported by the marked abnormalities seen in patients with Escobar

syndrome due to recessive mutations in the *CHRNA3* gene [6] causing fetal AChR γ subunit disruption. Absence of myasthenic features on neurophysiological assessments [1] and lack of response to acetylcholine esterase inhibitors in the chronic stages suggested that FARIS represented an “ingrained” endplate myopathy rather than an ongoing defect of neuromuscular transmission [1].

Salbutamol, a β_2 -adrenergic agonist commenced in our patient considering its proven efficacy in various neuromuscular disorders and lack of response to other treatments, resulted in dramatic and sustained improvement. Salbutamol is highly effective in genetic CMS due to mutations in several genes, most notably *DOK7* and *COLQ*, and has been demonstrated to improve AChR cluster assembly and NMJ architecture in a mouse model of anti-MuSK MG [7].

Taken together, our observation suggests salbutamol as an effective therapy for a potentially severe condition for which there is currently no treatment [1]. FARIS may provide a suitable model to study mechanisms of salbutamol action(s) also relevant to other neuromuscular conditions with disturbed NMJ architecture and/or function.

Level of Evidence:

This study provides Class IV evidence that salbutamol improves myasthenia-related signs in children with FARIS. This is a single observational study without controls.

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Figure legend

Figure 1

Facial features pre and post commencement of salbutamol treatment: Patient with Fetal Acetylcholine Receptor Inactivation Syndrome (FARIS) at 4 years 10 months of age. Facial features (A) before, (B) 24 hours after commencement of treatment with salbutamol 1mg three times daily, and (C) 24 hours after increase of salbutamol treatment to 2mg three times daily.

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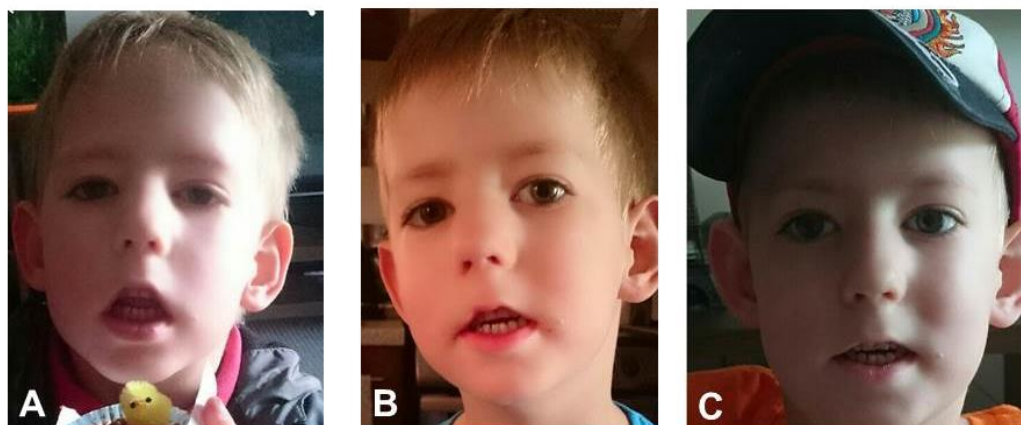


Figure 1

Patient with fetal acetylcholine receptor inactivation syndrome at 4 years 9 months of age. Facial features (A) before, (B) 24 hours after commencement of treatment with salbutamol 1mg 3 times daily, and (C) 24 hours after increase of salbutamol treatment to 2mg 3 times daily.